REMARKS

Summary of the Invention

The present invention features a novel protein belonging to the VEGF family (VEGF-D) and a gene encoding the protein. Specifically, the invention relates to an isolated VEGF-D protein encoded by an isolated nucleic acid hybridizing under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO: 2 wherein the protein has the biological activity of a VEGF family protein.

Summary of the Office Action

Claims 1 and 2 were examined in this case. Claims 1 and 2 stand rejected under 35 U.S.C. § 101, § 112, and § 102. The present response cancels claims 1 and 3-10 and amends claim 2. All objections and rejections raised in the Office Action are addressed individually below.

Support for the Amendments

Support for the phrase "under stringent conditions" is found in the specification at page 4, fourth paragraph. No new matter is added by these amendments.

Drawings

The Examiner notes that the drawings are objected to because Figure 4 should use

capital letters to denote the two individual panels. In addition, the Examiner notes that the Applicants should also correct the text of the specification to refer to Figures 4A and 4B using capital letters. Applicants note that such amendments have been made, as set forth above, and this rejection should be withdrawn.

Priority

The Examiner points out that an application in which the benefit of an earlier application is desired must contain a specific reference to the earlier filed application in the first sentence of the specification, as required under 37 CFR 1.78. Such priority information has been added and this rejection should be withdrawn.

Rejections Under 35 U.S.C. § 101

Claims 1-2 stand rejected on the assertion by the Examiner that the claimed invention is directed to non-statutory subject matter. The Examiner states that the claims fail to include any limitations which would distinguish the claimed proteins, peptides, and compositions from those which occur in nature.

Applicants point out that claim 1 has been canceled and claim 2 has been amended to recite "An isolated VEGF-D protein. . ." This amendment distinguishes the claimed protein from non-statutory subject matter and this aspect of the rejection should be withdrawn.

Claims 1-2 stand further rejected under 35 U.S.C. § 101 on the assertion by the Examiner that the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility. The Examiner asserts that the instant application does not disclose the biological role of this protein or its significance. Applicants disagree.

Claim 1 has been canceled, rendering the rejection to claim 1 under 35 U.S.C. § 101 moot. Claim 2 to has been amended to recite an isolated VEGF-D protein encoded by an isolated nucleic acid hybridizing under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO: 2 wherein the protein has a biological activity of a VEGF family protein.

The specification discloses that a gene having homology to VEGF-C was identified by searching against Expressed Sequence Tags (EST) and Sequence Tagged Sites (STS) in the GenBank database. Primers were designed based on the EST sequence and used to amplify and isolate the corresponding human cDNA using the 5' RACE method and the 3' RACE method. Sequencing of the cDNA revealed an encoded protein, human "VEGF-D," that is "highly homologous" to human VEGF-C (see page 2, third paragraph and page 12, lines 17-19). The specification further demonstrates that the VEGF-D nucleic acid was used to clone the mouse VEGF-D and the rat VEGF-D sequences (see Examples 7 and 9).

The function of the VEGF-D protein encoded by SEQ ID NO: 2 is clearly

disclosed in the specification. Specifically, the specification states that

> "[t]he protein of the present invention (VEGF-D) has significant homology to VEGF-C and can be considered to be a fourth factor of the VEGF family. Since the major function of VEGF is vascular formation . . . the protein of the present invention is thought to have similar functions."

These teachings are supported by findings published in recent journal articles (submitted herewith). For example Patanen et al. (*FASEB* 14:2087-2096 (2000)) state that "[b]oth VEGF-C and VEFG-D are also ligands for the VEGFR2/KDR receptor tyrosine kinase and can induce angiogenesis in certain experimental systems" (see page 2087, second column, last sentence of first paragraph). Korebayashiu et al. (*Jpn. J. Cancer Res.*, 90:977-981 (1999)) disclose that "VEGF-D can bind to and activate VEGFR-3" which they report is "a tyrosine kinase receptor which is predominantly expressed in the endothelium of lymphatic vessels" (see page 977, column 1, paragraph 2). As but another example, Achen et al. (*Eur. J. Biochem.* 267:2505-2515 (2000)) state that "[g]iven that VEGF-D activates receptors on vascular and lymphatic endothelial cells, it has been proposed that VEGF-D can stimulate the growth of blood vessels and lymphatic vessels into regions of the developing embryo or into tumours" (page 2505, second column, first paragraph).

The Examiner further points to the 27% homology of the protein of the invention with VEGF-C and appears to doubt the inclusion of VEGF-D as a member of the VEGF family. As noted above, the specification refers to the VEGF-D sequence as "highly

homologous" to the VEGF-C sequence (page 12, lines 17-19). Therefore, those skilled in the art recognized the 27% homology between VEGF-C and VEGF-D as having a high percentage of homology. This is evidenced by the naming of the protein as "VEGF-D." Furthermore, almost all research papers published recently refer to the protein of the invention as "VEGF-D" indicating that "VEGF-D" is the publically accepted term by those skilled in the art for this protein based on its homology to VEGF-C and its function in vascular formation (Patanen et al., *FASEB* 14:2087-2096 (2000); Korebayashiu et al., *Jpn. J. Cancer Res.* 90:977-981 (1999); Achen et al., *Eur. J. Biochem.* 267:2505-2515 (2000); Niki et al., *Clinical Cancer Research* 0:2431-2439 (2000)).

It is well known that a conservation in amino acid sequence between proteins (i.e., a conservation in protein structure) is likely to translate to a conservation in function between proteins. Such a conserved region exists in VEGF-D. For example, the last paragraph of Example 1 points to the homology between VEGF-C and VEGF-D and further states that "amino acids that are important for maintaining the protein structure, such as cysteine and proline were well conserved" (see Fig. 2).

In conclusion, Applicants assert that based on the specification, there is a substantial and credible utility for the claimed invention. Based upon the Applicants' disclosure, there is no reason to doubt the assertion that SEQ ID NO: 2 does not encode a VEGF family member protein that functions in vascular formation. Indeed, as set forth above, since the filing of the present application, experimental results in the field have

supported this finding. In addition, VEGF family member proteins have a well-established role in angiogenesis and lymphangiogenesis (see, e.g., Achen et al. Page 2505, column 2, second paragraph). In the present case, SEQ ID NO: 2 was shown to encode a VEGF family member protein (VEGF-D) that the skilled artisan would have recognized as having a specific, substantial, and credible utility based on its enzymatic activity.

In view of the above, withdrawal of this rejection is requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-2 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. This rejection has several aspects that will be addressed individually below.

The Examiner states that the instant claims are directed to (1) a protein having the amino acid sequence of SEQ ID NO: 1, (2) a protein having one or more substitutions, additions, deletions from SEQ ID NO: 1, (3) a protein encoded by a DNA which hybridizes to the DNA of SEQ ID NO: 2. The Examiner further states that claims 1 and 2 encompass "every protein in existence" and the specification fails to provide a representative number of species which support the broad genus which is being claimed.

As pointed out above, claim 1 has been canceled and claim 2 has been amended to recite an isolated VEGF-D protein encoded by an isolated nucleic acid hybridizing under highly stringent conditions to the complement of the sequence set forth in SEQ ID

NO: 2 wherein the protein has a biological activity of a VEGF family protein.

High stringency conditions are described in the specification at page 4, third and fourth paragraphs. One skilled in the art would certainly recognize that the human VEGF-D sequence could be used to routinely identify additional VEGF-D nucleic acid sequences, which encode additional VEGF-D proteins that have the biological activity of a VEGF family protein. A person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because highly stringent conditions set forth in the claim yield structurally similar DNAs. Indeed, the specification demonstrates the use of the human VEGF-D sequence to clone the mouse and rat VEGF-D cDNAs using hybridization, illustrating the presence of a representative number of species of the invention now claimed.

In conclusion, the representative number of species disclosed in combination with the coding function of DNA and the level of skill and knowledge in the art clearly enable the invention now claimed. Therefore, in light of the amendment to the claims and the teachings of the specification, this aspect of the rejection should be withdrawn.

The Examiner further states that the specification fails to provide a written description under 35 U.S.C. 112, first paragraph, of the species or the genus which are encompassed by the instant claims except for the protein of SEQ ID NO: 1. Applicants point out that the amendments to the claims are believed to overcome the present rejection. The specification teaches that "a person skilled in the art could routinely isolate

homologs of human VEGF-D of the present invention from other organisms by allowing the DNA shown by SEQ ID NO: 2, or part thereof, as a probe, to hybridize with the DNA derived from other organisms" (page 4, lines 3-7). The specification proceeds to teach of high stringency hybridization conditions at pages 4-5 and demonstrates the cloning of the mouse and rat VEGF-D protein encoding genes using similar hybridization conditions. Moreover, the function of VEGF family proteins is disclosed at page 3, lines 20-28.

In light of the above, withdrawal of this aspect of the rejection is requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1 and 2 stand rejected under 35 U.S.C. § 112, second paragraph, as failing to set forth the subject matter which applicants regard as their invention. The Examiner asserts that claim 1 is directed to a protein having the amino acid sequence of SEQ ID NO: 1 or in which one or more amino acids are substituted, deleted, or added, but there is no upper limit on the number of mutations, every single amino acid could be substituted, and any number of amino acids could be added or deleted. With respect to claim 2, the Examiner states that all DNA will hybridized under any given set of conditions, therefore, this claim encompasses all DNA in existence, and therefore, all proteins encoded by these DNAs. The Examiner questions whether the Application intended to claim a protein of SEQ ID NO: 1, and things that are related to this amino acid sequence.

In view of the present amendment, which cancels claim 1 and amends claim 2, the

present rejection should be withdrawn. Specifically, claim 2 has been amended to recite that the hybridization conditions are "highly stringent" hybridization conditions. Furthermore, claim 2 requires that the protein has a biological activity of a VEGF family protein, as set forth at page 3, lines 23-24. The claims, as amended herein, do not encompass all DNA in existence and the proteins encoded by these DNAs. The claims are now drawn to proteins encoded by a specific subset of VEGF-D DNAs that hybridize under highly stringent conditions to the VEGF-D nucleic acid of SEQ ID NO: 2 and that have the activity of VEGF family proteins.

In view of the above, the rejection under 35 U.S.C. § 112, second paragraph, should be withdrawn.

Rejections Under 35 U.S.C. § 102

The Examiner states that claims 1-2 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Claffey et al. (J. Biol. Chem. (1992)). Specifically, the Examiner states that Claffey et al. disclose a protein called VEGF that has one or more substitutions additions, or deletions in its amino acid sequence from that of SEQ ID NO: 1 of the instant application, therefore, it anticipates the instant claims. The Examiner further states that Claffey et al. teach that VEGF is encoded by a DNA which would hybridize to the DNA of SEQ ID NO: 2, absent evidence to the contrary.

The VEGF protein disclosed by Claffey et al., although a member of the VEGF

family of proteins is not a VEGF-D protein. Indeed, the VEGF protein disclosed by Claffey et al. is an entirely different protein, specifically, the VEGF-A protein. The VEGF-A protein is clearly set apart from the VEGF-D proteins of the present invention by the present amendment to claim 2. A protein that is not a VEGF-D protein would not be expected to hybridize to the nucleic acid sequence of SEQ ID NO: 2 under high stringency conditions. Thus, Claffey et al. does not contain every element of the claimed invention and is not anticipatory under 35 U.S.C. 102. This rejection should be withdrawn.

CONCLUSION

Applicants respectfully request reconsideration of the newly pending claims.

Enclosed is a petition to extend the period for replying for three months, to and including November 27, 2000, since November 26th falls on a Sunday. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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